6. Network Overview

i. Mission

The mission of the MTN is to reduce the sexual transmission of HIV through the development and evaluation of products, which reduce the transmission of HIV when applied topically to mucosal surfaces. The goal is to conduct scientifically rigorous and ethically sound clinical trials of microbicide safety and effectiveness, which will support licensure of these products.

The MTN will:

- Develop a highly focused microbicide development strategy based on a drug development model.
- Strive to maintain outstanding operational execution of protocol development and implementation, laboratory and data management support and fiscal oversight.
- Maintain a performance-oriented network culture.
- Create and maintain a fast, flexible leadership structure.
- Identify key talent and ensure that it is preserved and new talent is brought in.
- Keep network leaders committed to network business.
- Value innovation in clinical trial design, implementation and identifying correlates of safety and efficacy and share it with partners.

With almost 5 million new HIV infections in 2004, of which 90% were sexually transmitted, prevention of sexual transmission of HIV is one of the top public health priorities. Despite 20 years of vaccine research, progress towards identifying immunogenic vaccines has been slower than anticipated. Given the scientific challenges facing the HIV vaccine field, and the increasing proportion of new HIV infections that are occurring among women, new prevention strategies to reduce male-to-female HIV transmission are critically needed. One promising approach is topical microbicides, which are antimicrobial agents formulated for the application to the surface of the vagina and/or rectum for the prevention of HIV transmission during sexual intercourse. While the development and testing of topical microbicides for prevention of HIV might seem to be relatively straightforward, microbicide products are unlike most anti-infectives in that they will be used repeatedly with each act of intercourse over a period of many years. While topical application affords the advantage of providing lower systemic toxicity to the reproductive tract, it also requires an in-depth understanding of the genital tract mucosa, product-specific factors that increase local toxicity, and how that may enhance HIV risk. Further, unlike vaccines, acceptability of microbicide products to women and their sex partners is also of great importance because women must decide whether or not to use the products with each act of intercourse. The concept of developing topical antimicrobial agents for prophylactic use represents a natural extension of the use of topically applied agents for the treatment of vaginal infections and as spermicides. There are now numerous proof-of-concept studies in animal models documenting that topically applied agents such as PRO 2000/5/5 or PSC-RANTES can prevent SIV infection in a primate model. It is likely that over the seven years of the MTN we will be able to answer three questions:

- Can a microbicide, which can at least partially prevent HIV infection in women, be identified?
- How can we best measure safety of topically applied microbicides, which will be used over years of follow-up with each act of intercourse?
- Can we measure the acceptability of such products to women and their partners, and can we measure adherence and its impact on effectiveness

Current Status of Microbicide Trials

There are currently 6 trials which are evaluating the effectiveness of topical microbicides for prevention of HIV, and these are summarized in Table 1 below.

Table 1. Ongoing Efficacy Trials of Topical Microbicides

Sponsors	Product	No. Women Seen	No. Women to Enroll	Status	Complete
NIAID	BufferGel, PRO 2000/5/5	9000	3200	Ongoing	2007
Pop Council	Carraguard	12,540	6300	Ongoing	2005
FHI/USAID	Savvy	10,000	4284	Ongoing	2005
FHI/USAID	Cellulose sulfate	5000	2160	Ongoing	2006
CONRAD/USAID	Cellulose sulfate	5000	2574	Ongoing	2008
MDP/MRC	PRO 2000/5/5	20,000	12,000	2005	2008

The microbicide research community considers the identification of a safe and at least partially effective microbicide within our grasp in the next 7-10 years. While the development of a safe and effective microbicide is possible, it will require careful product selection based on many factors, including preclinical laboratory testing, streamlined clinical trial designs to assess safety and efficacy, and strategic use of increasingly limited resources.

During the MTN Leadership grant preparation, discussions were held with thought leaders inside and outside of the microbicide community. These discussions and written evaluations led to identification of key issues and lessons learned which the MTN leadership has considered. These issues, and how the MTN's proposed response is summarized below:

Issue: Lack of effective coordination between the DAIDS microbicide trials agenda and other funders in the microbicide field (comment from other funders).
MTN Response: A Microbicide Liaison Committee will be established, comprised of all of the major funders and microbicide leaders internationally and domestically. The objective will be to communicate regarding plans for both large and small trials, so that duplication and overlap will not occur. Further, innovations in clinical trial design and coordination of international infrastructure will be sought, as described in Section 9.

Issue: Need to focus on conducting research rather than building infrastructure (derived from the External Review for the HPTN, January 22-23, 2003)
MTN Response: The MTN proposes to focus most of its international research efforts within the African continent and to focus on established research sites with clinical and laboratory infrastructure. The MTN will assess international site access to treatment and referral of HIV infected individuals, which is necessary for the ethical conduct of microbicide trials.

Issue: To ensure a robust pipeline of microbicide products, there is a need to include Phase I clinical portfolio for new agents (from the HPTN External Review, January 2003).
MTN Response: A balanced clinical trial portfolio incorporates a large number of Phase 1 and 2 safety studies which will be run concurrently, efficiently utilizing domestic Phase I clinical trial site capacity. This will allow the MTN to assess a broader range of candidate microbicides internationally for evaluation in rank-selection trials (intermediate sized effectiveness studies of several thousand women).

Issue: Need a more formal strategy within the protocol development process to ensure that behavioral science is consistently incorporated into the development of protocols (from the HPTN External Review, January 2003).
MTN Response: A team of behavioral scientists spanning psychology to ethnography has been incorporated into the MTN. Further, a member of the behavioral science group will be a protocol team member on every MTN protocol. To enhance cross network coordination, the Behavioral Core of the HPTN, which has standardized tool kits for use in behavioral studies, will also be utilized.

Issue: There was poor communication and coordination between network leadership and DAIDS regarding the cost of trials and planning for out year financial resources (HPTN External Review, January 2003).
MTN Response: The new structure proposed by DAIDS ensures that the CORE leadership will manage protocol implementation funds. As summarized in the CORE application, estimates of study costs will be calculated on a per patient basis and payments will be linked with site performance. Importantly, all decisions regarding inclusion of sites and decisions regarding, which protocols will move forward, will have input from DAIDS representatives as part of the Executive Committee. It is anticipated that the direct fiscal management of protocol development and implementation funds using a hybrid NIH/drug development model will enhance communication between leaders and DAIDS.

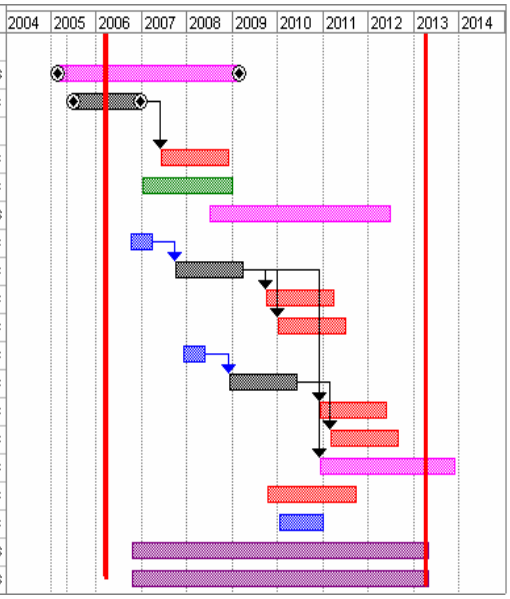
Issue: The HPTN research agenda was too broad to allow for efficiencies in protocol development since each protocol team required widely differencing expertise and background (this observation was made by PI's.
MTN Response: The MTN will have a highly focused research agenda on topical microbicides, adopting the approaches described in the SDMC that include focus protocol teams and CORE protocol physicians with face-to-face protocol team meetings to facilitate completion of protocol development.

Issue: The protocol development process was needlessly cumbersome, conducted primarily during conference calls and reliant on the responsiveness of PI's (concern noted by several site PI's, the central lab representatives and the SDMC).
MTN Response: The MTN proposes a protocol development model which is similar to that employed by the HVTN. Summarized briefly, this process requires that specific criteria be met prior to protocol development. Protocol physicians in the Pittsburgh Core Operations Center, and FHI protocol specialists will draft the initial protocol, which will then be developed within 60 days and finalized during a face-to-face 2-day meeting attended by all of the protocol members. Community representatives, behavioral scientists, and DAIDS representatives will be included in these protocol teams.

Issue: Study sites were not used effectively due to protocol delays (a comment made by several site PI's).
MTN Response: The MTN portfolio Gantt chart as shown in Figure 1 shows the framework for Phase I, 2, and 2B studies. If there is an unforeseen delay in a study due to lack of availability product, or unforeseen laboratory delays, the clinical trial sites can be engaged in alternative studies. This approach requires a range of clinical trial activity occurring simultaneously and proactive management of the clinical trial portfolio to ensure that all clinical trial sites are productively engaged.

Figure 1. MTN Clinical Trial Portfolio

ID	Task Name	Product (s)	Population	Phase	N	Duration
2						
3	HPTN-035	BG, Pro2000	HIV Neg	2B	3220	1040 days
4	HPTN-059	PMPA	HIV Neg	2	200	390 days
5						
6	MTN-001	PMPA	HIV Pos	1	45	390 days
7	MTN-002	N/A	HIV Neg	Prep	1500	520 days
8	MTN-003	TDF, PMPA	HIV Neg	2B	3000	1040 days
9	MTN-004	CCR5	HIV Neg	1	30	130 days
10	MTN-005	FI, CCR5	HIV Neg	2	300	390 days
11	MTN-006	FI	HIV Pos	1	45	390 days
12	MTN-007	CCR5	HIV Pos	1	45	390 days
13	MTN-008	RTI ring	HIV Neg	1	30	130 days
14	MTN-009	RTI, RTI ring	HIV Neg	2	300	390 days
15	MTN-010	RTI	HIV Pos	1	45	390 days
16	MTN-011	RTI ring	HIV Pos	1	45	390 days
17	MTN-012	RTI, FI, CCR5	HIV Neg	2B	4900	780 days
18	MTN-013	RTI	HIV Neg + HIV Pos	1	60	520 days
19	MTN-014	Rectal TBD	HIV Neg	1	30	260 days
20	MTN-015	N/A	HIV Pos	Seroconverter	300	1712 days
21	MTN-016	N/A	HIV Pos	Registry	225	1712 days



BG: Buffer Gel

FI: Fusion Inhibitor

CCR5: Chemokine Receptor 5 Antagonist

RTI: Reverse Transcriptase Inhibitor

Issue: There was not a formal mechanism for microbicide products to enter the network pipeline and there was a lack of standard product selection criteria (a comment from several product developers and investigators).
MTN Response: The MTN has proposed the development of a Microbicide Industry Liaison Committee. This committee chaired by the CO-PI, Dr. Ian McGowan will be in charge of actively identifying new microbicide products which can be brought into the MTN for evaluation, and coordinating activities with those sponsors to ensure that they are familiar with the processes involved in NIH-funded trials. These activities are summarized in Section 3b2 of the CORE application. For product selection process for microbicide trials, a Product Selection Committee has been established as one of the Core Resource Committees, which will include members of NIH, as well as members of the Central Laboratory in order to identify products that are likely to have optimal activity. Importantly, the Central Laboratory of the MTN has incorporated a standardized evaluation system for assessing the spectrum of activity against a broad range of HIV isolates, pharmacology, and toxicity in standardized preclinical assays. Thus, the MTN's microbicide product selection will not rely upon the data provided by the industry partner.

Issue: There was not consistent community input in protocol development (several comments from members of the community working group of the HPTN, also noted within the HPTN Evaluation 2004).
MTN Response: The MTN will include a member of a site community advisory group in each protocol team. This community member will come to Pittsburgh for the protocol development face-to-face meeting. This model has been developed by the VTN and has been found to be of benefit to the community members, who gain a much greater understanding of the protocol development process, and which enhances the quality of consistent community input at the earliest stages of protocol development.

Issue: There was a lack of communication across protocol teams, which lead to the perception that there was a need to "reinvent the wheel" with the development of each new protocol (comment from several site PI's).
MTN Response: There will be only four major types of protocols in the MTN. These include Phase 1 safety studies of HIV uninfected women, Phase 1 safety studies of HIV infected women, and extended safety studies of HIV uninfected women and Phase 2B effectiveness studies. Thus, heavily templated protocols will be developed and utilized for each proposed Phase of MTN clinical trial. This will ensure consistency across protocols, enhance the speed of protocol development and review, and facilitate a common protocol structure to which individual scientific studies can be added as ancillary substudies. All templates will be developed in the Phase 1/ 2 and 2B committees with the input of the protocol physicians located in the Pittsburgh Core.

Issue: Site budgets needed to be developed annually rather than for the lifetime of the protocol. There was significant variability in what was included in the HPTN site core budgets, which made calculation of a per patient protocol costs difficult. There was a perception that some sites had a more "padded" core budget than others (this observation was made by several HPTN site PI's and CORE).
MTN Response: The decision by DAIDS to develop a more structured site core budget model for the networks should help standardize the cost for core infrastructure across clinical trial units. In addition, the MTN will develop a process similar to the VTN in that MTN core budget specialists will prepare protocol draft budget templates in collaboration with protocol physicians to guide MTN CTUs in preparing site budgets for clinical trial costs. This is also similar to the industry model in developing core template budgets for clinical trial sites. For international sites, which may have widely different needs than domestic CTUs, the Regional Physicians will be consulted. Further, sites will have funding directly linked to the numbers of subjects enrolled and retained rather than in a fixed sum on an annual basis. This will allow core leadership to exert greater control and fiscal responsibility over network protocol implementation funds.

Issue: There was a lack of physician expertise within Core during HPTN. This was a problem since protocol specialists commonly encountered problems during protocol development and safety assessments during follow-up. These needed to be referred back to members of the study team who did not always have the appropriate expertise or knowledge, or an understanding of DAIDS or network policies (this comment from a domestic site PI and members of the SDMC).
MTN Response: Both protocol team physicians and safety physicians will be incorporated as part of the Core at the University of Pittsburgh. Safety studies require a thorough knowledge of colposcopy, and MTN Core Physicians will include obstetrician-gynecologists with specialized training in evaluation of colposcopy.

Physicians with training in infectious diseases/HIV and internal medicine will be incorporated within the study teams and CORE to provide assistance with developing standards for safety testing and HIV clinical management issues. Safety physicians located in Pittsburgh will work directly with the SDMC to review safety reports and will also participate in the safety teams for each of the proposed MTN protocols. By centralizing this medical expertise within the CORE, problems or trends, which emerge across protocols, can be dealt with expeditiously and in a standard manner. Further, there will be a single source of communication with the medical officers within the Division of AIDS to provide a more coordinated medical monitoring approach.

Issue: The network evaluation systems in place to monitor the operations of the CORE labs, data management, CORE support and site functions were not structured in a way that allowed "mid-course correction" (this comment came from members of all levels of the HPTN including a DAIDS representative).
MTN Response: Quantitative and qualitative measures will be used to perform an ongoing evaluation of every level of network function. Once established, this evaluation process will be designed to identify "best practices" in protocol development, implementation and study monitoring.

Issue: There was inadequate infrastructure support for clinical trial sites in developing countries, specifically Africa. Problems, which arose, needed to be handled by e-mail and/or over the phone during conference calls. However, the quality of communications was not always optimal and differences in time zones were a significant impediment to feedback to the sites. There was not always clear communication between the clinical trial sites and CORE regarding the problems, which were leading to protocol implementation (several site PI's).
MTN Response: The MTN has developed an innovative model to support international microbicide effectiveness trials in Africa, which will provide significant infrastructure support to assist international MTN sites and enhance coordination with the CORE. Dr. Connie Celum has developed a successful Regional Site Director model in the Gates-funded Partners in Prevention (HSV-HIV transmission) study, which has been adapted for the MTN. Regional physicians will be located in Kenya and South Africa to provide African physician support for clinical site development, community education, and protocol implementation. In addition, we plan to hire clinical research managers with prior CRO experience who will be based in Africa in order to provide additional timely, protocol-specific support for the operational aspects of protocol implementation, under the direction of the FHI Core Implementation Team. Finally, Regional Laboratory Managers will be based in Africa in collaboration with Johns Hopkins University to establish an enhanced system of laboratory training and support for the site laboratories, which has required intensive development at international HPTN sites. A staff member from the University of Pittsburgh Central Lab will be tasked with interacting with the Regional Lab Managers and providing assistance with importation of shared lab reagents.

Issue: Many of the people involved in developing the microbicide trials and overseeing implementation were pulled in too many directions and resulted in delays (this comment from both domestic & international site PI's).
MTN Response: The MTN recognizes that development of microbicides through a regulatory pathway towards licensure by the FDA requires a drug development paradigm. The successful implementation of a drug development paradigm requires significant support, resources and dedicated staff who are focused on moving specific protocols forward and who are held accountable for failure to meet timelines. To accomplish this in the MTN, the staffing levels are significantly higher than the HPTN, but not as large as those used traditionally in pharmaceutically sponsored studies. The model of enhanced levels of fulltime staff devoted specifically to protocol development and implementation within the microbicide research agenda will be essential in meeting the aggressive timelines presented in the MTN application and will be more cost-effective since sites and protocol teams will be less likely to experience long delays.

Strategic Position

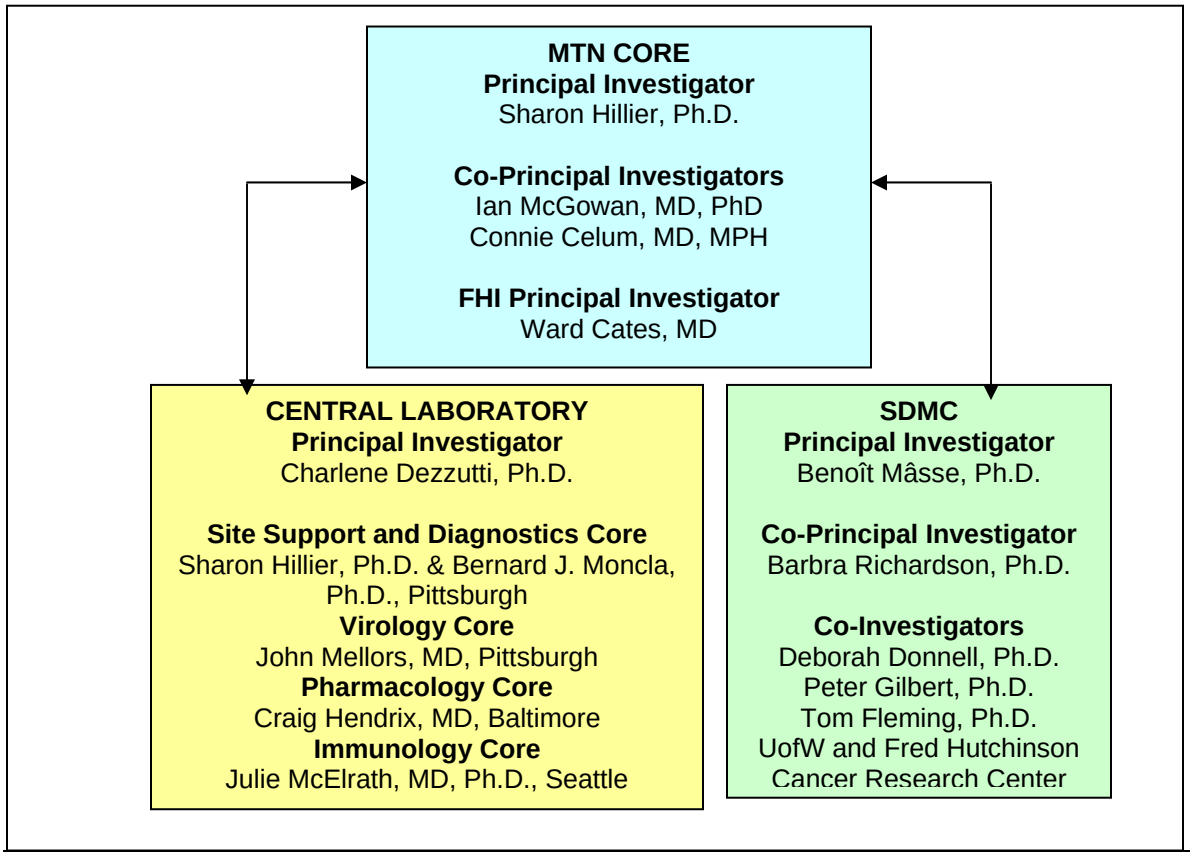
The MTN views their strategic position in the field of microbicides directed toward development of topical microbicides with specific activity against HIV. Thus, the primary types of products, which will be pursued by the MTN will be reverse transcriptase inhibitors, CCR5 antagonists, fusion inhibitors and other molecules which emerge and are likely to have a high degree of specificity against HIV. The decision to focus on HIV-specific compounds also requires that additional attention be paid during the studies to selection of resistant virus in intercurrent infections and the relative efficacy and selective pressure with different clades in infected women. Thus, an Antiretroviral Resistance Subgroup has been formed as part of the Science Committee, chaired by

Dr. John Mellors specifically for these issues. Further, a seroconverter protocol (MTN-015) has been developed by Dr. Connie Celum, which will prospectively follow all women who seroconvert during their participation in MTN studies.

ii. Organization

The proposed Principal Investigator for the MTN is Dr. Sharon Hillier, a Professor of Obstetrics, Gynecology and Reproductive Sciences and Molecular Genetics and Biochemistry at the University of Pittsburgh School of Medicine. Described in detail in Section 2b of the CORE network application, Dr. Hillier has extensive experience within the HPTN in development and implementation of the microbicide research agenda. Two Co-Principal Investigators for the MTN will include Dr. Ian McGowan, an Associate Professor at UCLA and Dr. Connie Celum, a Professor of Medicine at the University of Washington in Seattle. These two Co-Principal Investigators have experience complementary to that of Dr. Hillier. Dr. McGowan has extensive product development experience within the pharmaceutical industry and Dr. Celum has led large multi-center studies for HIV prevention in Africa and Latin America. The CORE activities will be primarily located at the University of Pittsburgh and will be directed by Dr. Sharon Hillier. The implementation of protocols will be directed through Family Health International under the direction of Dr. Ward Cates. International site support through a regional physician model will be coordinated by Dr. Celum at the University of Washington, and oversight of the domestic Phase 1 activities, manuscript preparation and science coordination will be entered at UCLA. Charlene Dezzutti who is currently a Senior Research Scientist at the Centers for Disease Control and Prevention but who will be joining the faculty at the University of Pittsburgh during the fall of 2005 will direct the Central Laboratory of the MTN. The Central Laboratory of the MTN will have a total of 5 cores which include the "Product Evaluation Core" which will be directed by Dr. Dezzutti and assisted by Dr. Lisa Rohan, Site Support Core and Diagnostics CORE directed by Drs. Sharon Hillier and Bernard Moncla, and a Virology Core directed by Dr. John Mellors. All of these Central Laboratory core activities will be headquartered in Pittsburgh. Two additional Cores including the Pharmacology Core, Dr. Craig Hendricks at Johns Hopkins University in Baltimore Maryland and the Immunology Core, Julie McElrath at the University of Washington in Seattle and also proposed.

Figure 2. MTN Organizational Structure



Dr. Benoît Mâsse of the University of Washington and the Fred Hutchinson Cancer Research Center will direct the MTN SDMC. Dr. Barbra Richardson will be the Co-PI. Other key personnel included from the statistical data management center will include Deborah Donnell, Ph.D., Peter Gilbert, Ph.D., Thomas Fleming, Ph.D., Thomas Darden, Ph.D., Gwen Glaefke, Thomas Skillman, Ph.D. The members of the statistical data management center are affiliated with SCHARP at the Fred Hutchinson Cancer Research Center in Seattle.

MTN Clinical Trial Portfolio Timelines

The MTN proposed clinical studies are summarized in Table 2 below and are described in greater detail in the research plan of the Core application. It is proposed that the MTN will be assuming the oversight for the completion of two ongoing HPTN trials, specifically HPTN-035 and HPTN-059. HPTN-035 is the Phase 2B effectiveness study of BufferGel and PRO 2000/5. The study was initiated during the first quarter of 2005 and thus will be ongoing at the time of the proposed start date for the new MTN leadership in March 2006. HPTN-035 is estimated to be completed in the fourth quarter of 2008.

Table 2. Summary of MTN Clinical Studies

Study Number	Development Phase	Enrollment (N)	Duration (Years)	Start	Finish
HPTN-035	2B	3220	4	Q1 2005	Q4 2008
HPTN-059	2	200	1.5	Q3 2005	Q4 2006
MTN-001	1	45	1.5	Q3 2007	Q4 2008
MTN-002	Prep	1500	2	Q1 2007	Q1 2009
MTN-003	2B	3000	4	Q3 2008	Q2 2012
MTN-004	1	30	0.5	Q4 2006	Q2 2007
MTN-005	2	300	1.5	Q4 2007	Q1 2009
MTN-006	1	45	1.5	Q4 2009	Q2 2011
MTN-007	1	45	1.5	Q1 2010	Q3 2011
MTN-008	1	30	0.5	Q1 2008	Q3 2008
MTN-009	2	300	1.5	Q1 2009	Q3 2010
MTN-010	1	45	1.5	Q1 2011	Q3 2012
MTN-011	1	45	1.5	Q2 2011	Q4 2012
MTN-012	2B	4900	3	Q1 2011	Q4 2013
MTN-013	1	60	2	Q4 2009	Q3 2011
MTN-014	1 (Rectal)	30	1	Q1 2010	Q4 2010
MTN-015	Seroconverter Study	300	6.5	Q3 2006	Q1 2013
MTN-016	HIV+ Registry	225	6.5	Q3 2006	Q1 2013

HPTN-059 is an extended safety study of 200 women evaluating coitally dependent versus daily use of tenofovir gel. The study is being conducted in New York City and Pune India and Dr. Hillier is the Protocol PI for this extended safety study. It is scheduled to begin enrollment during the third quarter of 2005 and will be completed at the end of 2006.

The rationale for transitioning oversight of these two large trials from the HPTN to the MTN lies primarily in the fact that the microbicide expertise in the HPTN will transition to the new MTN network structure. Every effort will be made to create a seamless transition for these two trials from HPTN to MTN oversight. The Central Laboratory support, the statistical data management support and the operational support at FHI will be maintained during the completion of the proposed studies. In addition to completing these two HPTN trials, the network leadership proposes a total of 16 new studies. The preparedness study of 1500 women is proposed for initiation in the first quarter of 2007, or approximately 9 months after the funding of the MTN. The purpose of the preparedness study (MTN-002) is to assess the 'trial readiness' of new MTN CTUs, which are anticipated to be funded during the network recompetition. The objective of MTN-002 is to develop a better assessment of the site's recruitment and retention strategies, current HIV seroincidence to inform the sample size and site capacity for effectiveness studies, and to ensure the readiness of the sites for performing laboratory research under GLP and clinical research under GCP standards.

The first major flagship protocol to be taken under the MTN will be a head-to-head comparison of oral versus vaginal tenofovir for prevention of HIV. This will be a double-blinded, randomized, placebo-controlled trial having three arms (active oral TDV plus placebo gel, placebo oral drug plus active TDV gel, and double placebo oral and gel products). This study (MTN-003) would be scheduled to begin in the third quarter of 2008 and would be scheduled for completion in the second quarter of 2012. New clinical trial unit sites identified for trial readiness during the preparedness study (MTN-002) as well as clinical trial sites completing HPTN-035 that successfully met HPTN-035 recruitment, retention, and implementation parameters would be transitioned into the MTN-003 study of oral versus vaginal tenofovir.

Within six months of the funding of the MTN sites, it is anticipated that the first Phase 1 safety studies will be launched in domestic MTN sites to evaluate new microbicide products. In order to move several products forward concurrently through the earliest stages of testing for safety in infected and uninfected women, as well as extended safety, it will be essential that domestic trial sites have the capacity to rapidly initiate and complete safety studies. Two extended safety studies have been proposed to evaluate different dosage forms of proposed microbicides (e.g. ring or gel) or dosing frequencies (e.g. daily dosing or coitally dependent dosing).

At the completion of the primary and extended safety studies, the network proposes a second Phase 2B study comparing three leading candidates and a placebo arm. This rank-selection trial is designed to provide an early assessment of the relative effectiveness of different classes of microbicide products, and to identify the product with the lowest number of endpoints to move into Phase 3 testing for licensure. Every effort will be made to bring different classes of microbicide products into the network and move these rapidly through Phase 1 and 2 safety testing to ensure that adequate number of products can be compared head-to-head. It is anticipated that the classes of products chosen to move forward will include, at a minimum, a fusion inhibitor, a reverse transcriptase inhibitor and a CCR5 antagonist. The specific microbicide products chosen to move forward into each of these studies and to the ranking trial of effectiveness will be ascertained collaboratively with the Division of AIDS and with the input of the Microbicide Product Selection Committee.

The microbicide products which will move forward to eventual licensure will need to be evaluated in adolescent populations to ensure that FDA labeling will allow their use in this high risk population. For this reason, the MTN has elected to collaborate with the Adolescent Trials Network (ATN) to evaluate products that are moving forward into the Phase 3 licensure trial to assess specific safety data in HIV infected and uninfected adolescents. MTN-013 is proposed as a Phase 1 safety study in adolescents in collaboration with the MTN, with an estimated timeline of 2009 to 2011 and inclusion of a minimum of 60 high-risk adolescent women. Finally, any microbicide product, which is moving forward to licensure, should be evaluated for safety during rectal use. The development of microbicides for rectal use is not a primary area of focus for the MTN. However, it is acknowledged that a substantial minority of women report anal intercourse. Therefore, at least some safety data with anal rectal exposure is needed to ensure that appropriate labeling can be provided to future users regarding the safety or toxicity of these products if used during anal intercourse. A single study of rectal microbicide safety to be conducted in women is proposed in the first quarter of 2010 (MTN-014).

MTN-015 is a seroconverter protocol, which will span from the third quarter of 2006 when MTN is funded through the first quarter of 2013 when the funding for the MTN is scheduled to end. The goals of the seroconverter study are to provide extensive follow-up and assessment of long-term safety for women enrolled in microbicide trials. Women enrolled in the seroconverter study will be evaluated for viral load systemically and in the genital secretions and will be evaluated longitudinally throughout the life of the MTN. An additional longitudinal observational study (MTN-016) provides a mechanism to collect additional data on HIV-infected women who are exposed to microbicides during the conduct of MTN studies. HIV-infected women are enrolled in safety studies but the length of follow-up for these women is short (four months). However, it is important to ascertain the long-term impact of topical microbicide exposure on resistant viral subtypes and their persistence over time. Therefore, HIV infected women who consent to be followed for longer periods of time will join a registry of HIV-infected women exposed to microbicides (MTN-016), which will provide a mechanism to do genotyping of the viral populations among women who received active product versus placebo.
The proposed timelines for the MTN portfolio are shown in Figure 1 above.

Over the course of the proposed funding period for the MTN we propose the completion of a large immediate proposed trial, HPTN-035, the initiation of preparedness studies (MTN-002) for the next 2B Phase study and the completion of the 2B Phase study of oral versus vaginal tenofovir (MTN-003), completion of a series of early and extended safety studies and the initiation of a third Phase 2B study (MTN-012). Over the course of the proposed MTN period of support, in excess of 12,000 women will be enrolled or followed in effectiveness studies, 600 will be enrolled in extended safety studies and nearly 300 will be enrolled in Phase 1 safety studies.

Executive Committee:

MTN seeks to establish a more streamlined structure which we hope will lend increased productivity while ensuring scientific integrity. The proposed Executive Committee Leadership is as follows:

Table 3. Proposed Executive Committee Membership

Member	Role in MTN	Voting	Rotating
Sharon Hillier	PI, MTN	YES	NO
Ian McGowan	Co-PI, MTN	YES	NO
Connie Celum	Co-PI, MTN	YES	NO
Ward Cates	FHI CORE PI	YES	NO
To be named	Pittsburgh CORE Operations	YES	NO
Ben Mâsse	SDMC PI	YES	NO
Charlene Dezzutti	Central Lab PI	YES	NO
Lisa Maslankowski	Chair, Phase 1/2 Committee	Yes	NO
Salim Abdool Karim	Chair, Phase 2B/3 Committee	YES	NO
DAIDS Representative	Sponsor	YES	NO
To be named	Community Representative	YES	YES
To be named	Domestic CTU Representative	YES	YES
To be named (n=2)	International CTU Representatives	YES	YES
Susan Cu-Uvin	AACTG – Women's Committee Chair	NO	YES

The Executive Committee will include a Community Representative who will rotate on a three-year schedule. Domestic and international representatives of CTUs who could be the site PI of the CTU or the microbicide PI at that CTU will be elected under rules outlined in Section 2 of the Core proposal. In addition, the Women's Committee Chair for the Adult AIDS Clinical Trials Group will be a member of the Executive Committee on a non-voting basis, which will help ensure the cross-work collaboration referral of women

Co-PI for Safety and Early Clinical Assessment:

The Co-PI for Safety and Clinical Assessment oversight is Dr. Ian McGowan of UCLA. As shown in Figure 4, Dr. McGowan will also chair the Industry Partnership Committee, which is tasked with identifying new molecules for evaluation in the MTN and coordinating the portfolio of microbicide products with industry sponsors. Within the Safety and Early Clinical Assessment Group is the Phase 1/2 Safety Committee, which will be chaired by Dr. Lisa Maslankowski, MD. The Phase 1/2 Safety Committee will develop the protocol templates for Phase 1 and 2 expanded safety studies. Further, the Phase 1/2 Safety Committee will make recommendations to the EC regarding matching clinical trial sites to protocols and to monitor the progress of these protocols through early and later safety studies. The Phase 1/2 Safety Committee will also advise the Executive Committee on the relative scientific value of ancillary studies or assays, which may be included as additional scientific comments for the templated protocols.

Co-PI for Effectiveness Studies

Dr. Connie Celum will oversee the portfolio of clinical study activities associated with effectiveness studies. As shown in Figure 3, Dr. Ken Mayer will chair a Preparedness Study Committee. The preparedness studies will be designed to identify population characteristics in proposed Phase 2B clinical trial sites, which give an early indication of the site's ability to recruit and retain women with the highest risk characteristics. In addition,

preparedness studies will provide a measurement of HIV seroincidence prospectively and through cross-sectional samples, using the STAHRS and avidity/affinity assays in collaboration with Dr. Susan Buchbinder and the Sexual Exposure and Risk Estimation committee. These data will inform the Phase 2B/3 committee chair regarding the site-specific capacity and characteristics of study populations for participation in Phase 2B and 3 studies.

The Phase 2B/3 effectiveness study committee chair will be Dr. Salim Karim who is currently the Protocol Chair for HPTN-035. The Phase 2B/3 committee will assist in the development of the Phase 2B effectiveness study template, will consider protocol design elements developed by other microbicide networks, and will develop criteria for the advancement of products from Phase 1 into the Phase 2B or Phase 3 trials. The Phase 2B/3 committee will also monitor the availability of MTN resources including finances, site capacity and scientific investigators and to ensure that they are most efficiently utilized in support of the MTN research portfolio.

MTN CORE Resource Committees

The Chairs of the QA/QC Committee, the Training and Education Committee, the Performance Evaluation Committee and Network Community Advisory Board Committee and the Site Management in Clinical Care Committee will be named from among investigators at the Clinical Trial Units. These CORE Resource Committees will provide an opportunity for CTU investigators to participate as network resource chairs. The activities of the QA/QC Committee, the Training and Education Committee, the Performances Evaluation Committee, and the Network Community Advisory Board Committee will also be coordinated through the Family Health International Core in North Carolina. Operationally, this means that there will be designated staff within FHI who will be responsible for generating the data and/or reports to be shared with other networks for resource committee meetings. The site investigators who chair these resource committees will work collaboratively with FHI staff to configure the reports and alter the collection methods in response to the findings and approaches presented at the CORE Resource Committee meetings among the networks.

The Study Monitoring Committee will be chaired by Dr. Tom Fleming and will be responsible for providing ongoing assessment of clinical trial sites and protocol teams in meeting recruitment goals, achieving retention targets and delivering the data by the specified timelines. A Manuscript Review Committee will be chaired by Dr. Ian McGowan and will be responsible for the timely development of MTN manuscripts.

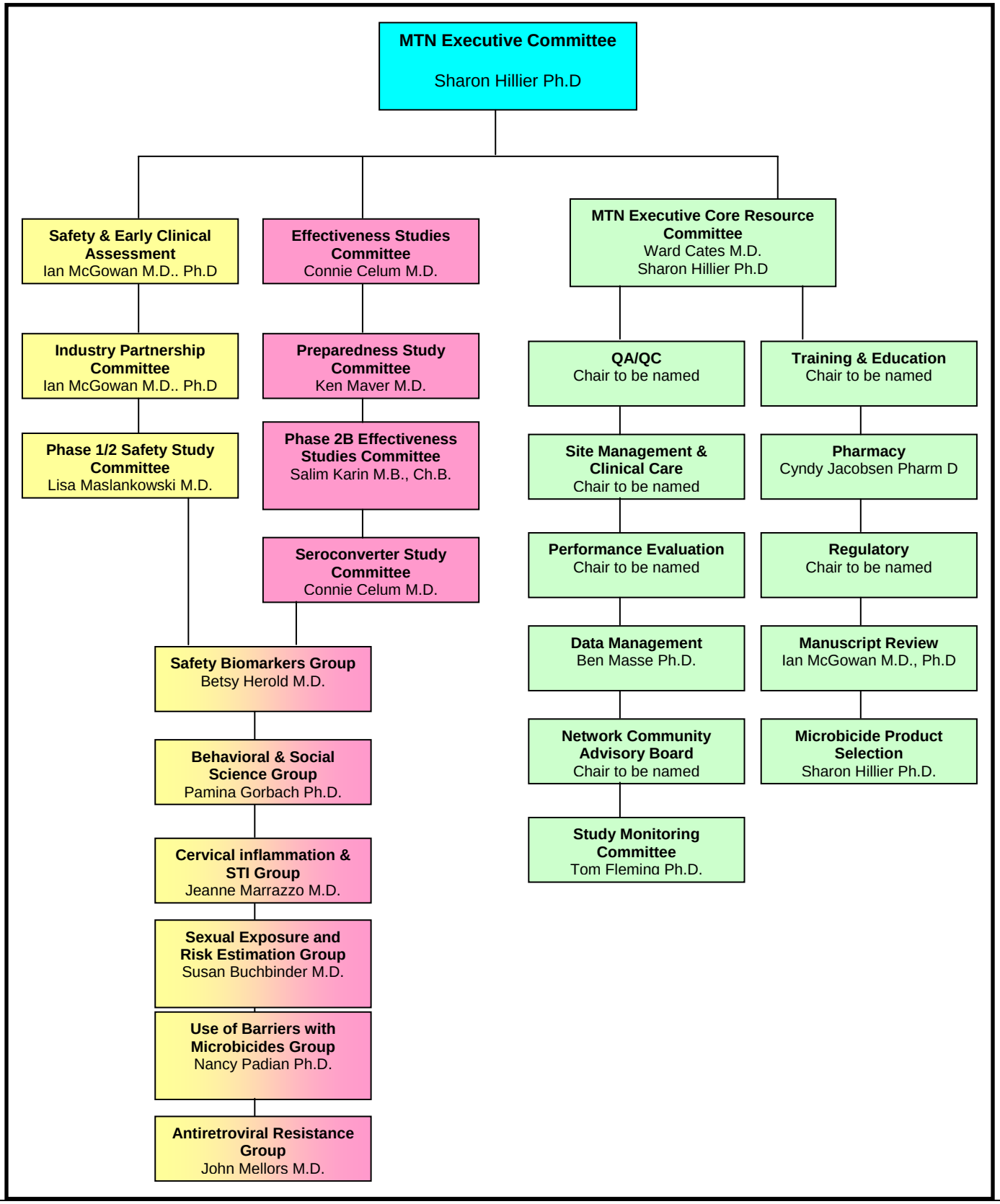
An essential piece of the MTN Core Resource Committee structure will be the Microbicide Product Selection Committee, which will be chaired by the MTN PI. Because each effectiveness study of microbicides involve several thousand women and cost millions of dollars, careful selection and judicial use of standardized criteria for evaluating products to move forward into the MTN portfolio are needed. The Microbicide Product Selection Committee will include members of the Central Laboratory, the Industry Liaison Committee, the Co-PI for Effectiveness Studies, the Chairs of the Phase 1, 2, and 2B/3 Committees and the Virology Core director. An innovation in the MTN is the utilization of standardized testing using explants and a wide array of viral strains to provide side-by-side comparison of multiple microbicide products. This type of in vitro assessment is not available to most industry partners and is not typically part of any IND package prepared by a corporate sponsor.

Science Committees

A total of 6 groups comprise the Science Committee for the MTN (Figure 3) and investigators having specific expertise in those areas chair each of the groups. Each of the scientific groups has proposed hypotheses and approaches for evaluating some aspect of their scientific research area within the clinical trial portfolio. The most important priority of the MTN is to move microbicide trials efficiently through the development and implementation stages. Thus, an overarching principle will be that no scientific studies will be added which hinder the implementation of the protocols, and that any additional costs or procedures need to be carefully justified and weighed by the MTN Executive Committee. However, it is also imperative that clinical trials proposed by the MTN lend more than simple answers of safety and effectiveness. Rather, it is critical that scientific substudies embedded in the protocols will provide new information on assessment of safety, implementation, product acceptability and adherence, how best to estimate sexual exposure, how women integrate the use of barriers with microbicides and the impact of microbicide use on antiretroviral resistance. Because acceptability and adherence are such important components of microbicide development, the

Behavioral and Social Sciences Group of the MTN Science Committee comprised of four different behavioral scientists each of whom brings different perspectives and indications to the team. The proposed scientific hypothesis, aims and approaches for each of the science groups have been provided in a Core application Section 1.

Figure 3. MTN Committee Structure



Proposed Clinical Trial Units

Potential sites for inclusion in the MTN were solicited during February 2005. Each of the MTN sites was asked to complete an MTN site questionnaire. Domestic sites were ranked according to past microbicide experience, capacity to conduct microbicide Phase 1 and 2 studies, previous participation in DAIDS sponsored network trials, ability to enroll participants within 6 months and other factors including past experience in microbicide research studies or unique clinical populations. The following is a list of the domestic clinical trial units, which are listed in the Core application for consideration as domestic clinical trial sites.

Table 4. Proposed Domestic Clinical Trials Units for the MTN

Administrative Component	CTU PI	Institution	Current DAIDS Network?	Experience in Microbicide Trials
University of Pennsylvania	Lisa Maslankowski, MD	University of Pennsylvania School of Medicine	YES	Phase 1 & 2
University of Pittsburgh CTU	John Mellors, MD	University of Pittsburgh, Pittsburgh, PA	Yes	Phase 1 & 2
Emory HCTU	Jeffrey Lennox, MD	Emory University School of Medicine, Atlanta, GA	Yes	Phase 1
Miriam Hospital	Timothy Flanigan & Ken Mayer	Miriam Hospital, Brown University	Yes	Phase 1 & 2
Case Western Reserve University	Michael Lederman, MD	Case Western Reserve University, Cleveland, OH	Yes	No
Columbia Consortium CTU	Wafaa El-Sadr, MD	Bronx-Lebanon Hospital & Columbia University	Yes	Phase 1 & 2
Indiana University	Ken Fife, MD	Indiana University	Yes	No

International MTN Clinical Trial Unit Sites were evaluated based on the responses provided in their site questionnaire regarding past microbicide experience, capacity to provide large clinical trials for effectiveness, past participation in DAIDS network studies, availability of HIV seroincidence data, the ability to enroll participants within 6 months of having a finalized protocol and other factors such as PI expertise. The following is a shortened version of the international clinical trial sites, which met the minimal criteria for participation in the MTN network. These sites are described more fully in the Core application Section 5.

Table 5. Proposed International CTU's

Administrative Component	CTU PI	Institution	Current DAIDS Network?	Experience in Microbicide Trials
Medical Research Council	Gita Ramjee, Ph.D.	Medical Research, Council, Durban, South Africa	YES	Phase 1, Phase 2 & 2B, Phase 3
Reproductive Health Research Unit	Helen Rees, OBE	Reproductive Health Research Unit (RHRU), University of Witswaterstrand, Johannesburg, South Africa	Yes	Preparedness & Phase 2
Infectious Diseases Epidemiology Unit	David Coetzee, MD	School of Public health & Family Medicine, Univ of Cape Town, South Africa	No	Phase 3
UCSF-UZ Clinical Trials Unit	Mike Chirenje, MD, FRCOG	UCSF, SF Univ of Zimbabwe	Yes	Phase 2B
To be determined	Elizabeth Bukusi, MD	KEMRI/UNIM-Kisumu, Kenya	No	Male efficacy trial
Makere Univ Johns Hopkins Univ (MU-JHU)	Laura Guay, MD	Johns Hopkins University	Yes	Phase 1
Johns Hopkins	Taha Taha, MD, Ph.D.	Johns Hopkins University	Yes	Phase 2B

Univ/Malawi College of Medicine	(Lilongwe and Blantyre)			
Univ of Kwazulu Natal (UKZN) CAPRISA CTU	Salim Abdool Karim, MD	Centre for the AIDS Programme of Research in South Africa (CAPRISA)	Yes	Phase 2B
Moi Teaching & Referral Hospital, Eldoret	Edwin Were, MB ChB, MS (Ken Fife)	Moi University, Eldoret, Kenya	Yes	No
Centre for Infectious Disease Research Zambia (CIDRZ)	Jeff Stringer	University of Alabama, Birmingham	Yes	Phase 2B
Harvard-Tanzania CTU	Wafaie Fawzi, MD, DrPH	Harvard School of Public Health	Yes	Phase 2B
National AIDS Research Unit	Sanjay Mehendale, MD, MPH	NARI, Pune, India	Yes	Phase 1 & 2
University of Nairobi	James Kiarie, MD, MPH	University of Nairobi & Washington	Yes	No

The CORE Operations Center

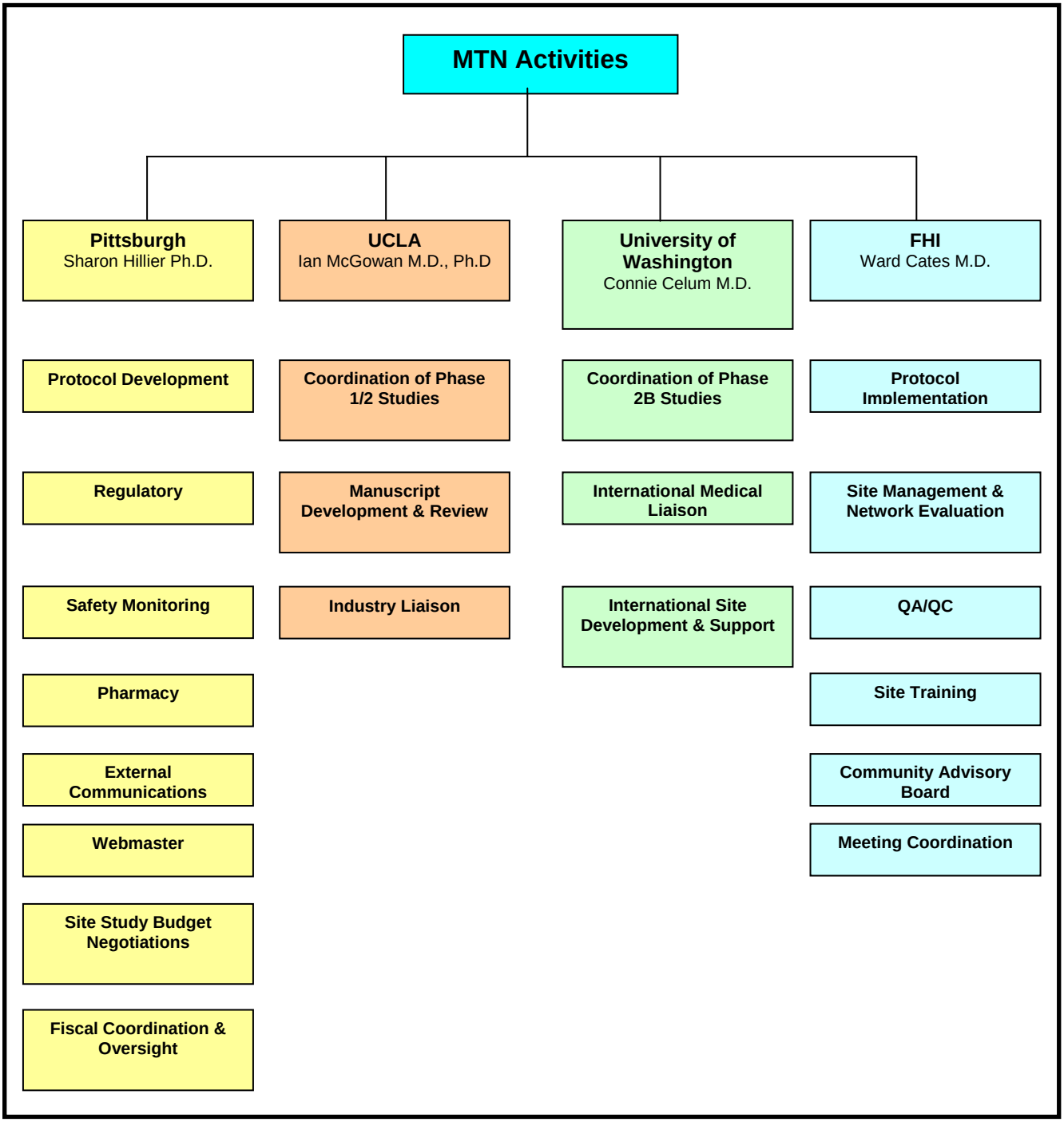
As described above, the CORE Operations Center will be spread over four geographic locations in Pittsburgh, Los Angles, Seattle and North Carolina. The primary responsibilities of the MTN CORE groups are outlined in Figure 4 below.

A complete description of the activities within each of the CORE groups is provided in the CORE application Section 3.

The SDMC – Statistical Collaboration and Methodologic Research

The Statistical Center for HIV/AIDS Research & Prevention (SCHARP) of the Fred Hutchinson Cancer Research Center (FHCRC) and affiliated faculty at the University of Washington provides statistical, operational and data management expertise for HIV vaccine, microbicide, and prevention trials. As the incumbent SDMC in the MTN/HPTN, this experienced team is familiar with site capabilities and establishing the information technology infrastructures needed to ensure data integrity and efficient transfer of data from site to SDMC. They are also responsible for many QA/QC and training functions in the network. SDMC staff are leaders in protocol design, study oversight, data analysis, and manuscript preparation. A major benefit to the MTN is the proposed involvement of the SDMC with two other prevention-oriented networks (HVTN, HPTN) such that prevention sciences data management are coordinated and synergized within a single grantee. Since this has been the case for the HVTN and the HPTN already, both networks benefit from the experiences of the other. An overarching goal of the MTN SDMC will be to provide statistical collaboration of the highest quality for all MTN-related research endeavors. To ensure that statistical issues are identified and addressed throughout network activities, faculty-level biostatisticians will be integral members of all microbicide development teams, protocol teams, laboratory science research network scientific reviews and oversight committees. This comprehensive engagement in the network research program will provide MTN statisticians with a broad perspective and allows identification of common statistical themes around which MTN study designs and analytic methods can be standardized. Methodologies will be operationalized in the form of SOPs and templates that prescribe statistical sections of trial protocols and statistical analysis plans; standardized and validated computer programs for study design calculations, data analyses and generation of routine study monitoring reports employed by the MTN SDMC. Broad engagement by SDMC statisticians in network activities will also provide the opportunity to identify and prioritize problems for which standard statistical solutions are not available or, if available, are not optimized to MTN needs. SDMC statisticians will engage in a robust program of biostatistical methodologic research driven by this stream of problems that have highest

Figure 4. Primary Responsibilities of MTN Core Groups



priority to and direct impact on MTN research activities. A system of statistical working groups, communicating directly with MTN clinical and laboratory researchers, will be organized around the more substantial of these methodology problems.

SDMC Structural Organization

The SDMC organization is characterized by SCHARP Study Teams led by a SCHARP project manager who manages SDMC aspects of the trial from implementation through to final analysis. The SCHARP project manager works directly with their counterparts in the Network CORE and Lab offices and a SDMC Senior Statistician assigned to each study. Study Teams are overseen by network affiliated SCHARP Senior Project

Managers, very experienced clinical trialists who provides technical direction to the Study Teams, provide rapid problem solving and be a key liaison to their counterparts in the CORE. The SCHARP Senior Project Managers have direct access to the Executive Leadership Group (ELG) of SDMC, to speed problem solving and enhance the responsiveness to the Networks.

SDMC Functional Organization

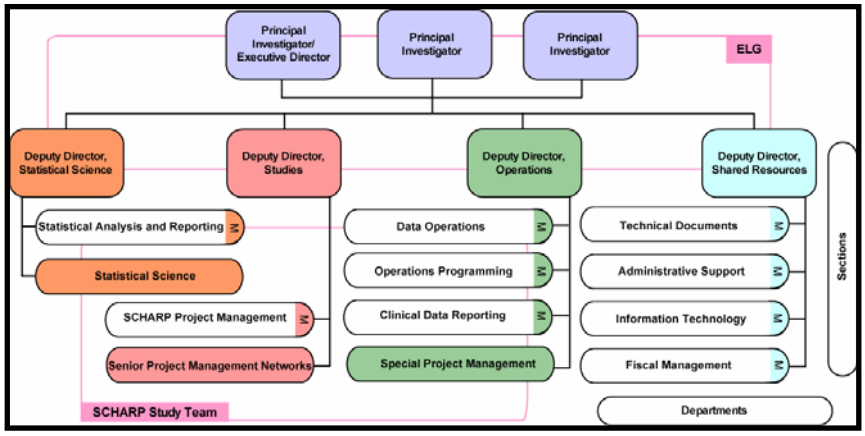
SCHARP is the SDMC for the HVTN and HPTN and is applying to be the SDMC for the MTN. Functionally; the SDMC is divided into 4 Departments with 12 Sections (Figure 5). Staff from 6 groups outside the project management department comprise the Study Team: statistical sciences, statistical analysis and reporting, data operations, operations programming, clinical data reporting and technical documents. The other Sections support non-study-specific aspects of SDMC activity, e.g., IT support, fiscal oversight, technical document production and administration.

The SDMC Internal Study Team

The SDMC internal Study Team will serve as the key cross-function organizational unit working within the SDMC and be a sub-unit of the larger MTN study team with includes members from CORE and Lab. The SDMC Study Team manages those aspects of the study that occur within the SDMC (For example, CRF design, clinical database and clinical monitoring set up, randomization system development, standard report setup, etc.) and works with the MTN team to assure that other aspects of the trial necessary for start up are accomplished in a timely fashion.

Studies Department

Figure 5. SDMC Organizational Structure



This small group consists of the Senior Project Managers, Project Managers and Project Assistants. Senior PMs are experienced clinical trial specialists who oversee a cluster of trials within the same Network. Project Managers are given the authority and responsibility to lead the team in aspects of trial design, operation and closeout that are the responsibility of the SDMC. Responsibilities include: (i) ensuring that SCHARP meets its obligations in accordance with Good Clinical Data Management Practices (GCDMP); (ii) ensuring timely development of DataFax setup, randomization system, product labeling, study database, DataFax/SAS edit checks, CRF and study materials, study-specific training materials/plan, safety reporting system, statistical analysis/reporting plan, specimen collection and labeling, shipping and storage plans, laboratory results data receipt procedures and study closeout; and (iii) serving as primary SDMC operational liaison with affiliated programs and institutions (e.g., CORE, Network laboratories, DAIDS, protocol chair, manufacturer).

Science Department

The Science Department is composed of 2 Sections. Faculty Statisticians hold either University of Washington or FHCRC faculty appointments. The Statistical Analysis and Reporting Section includes the Statistical Research Associates (SRAs), who are masters-level statisticians. This group (i) provides biostatistical leadership on research directions and study design; (ii) develops innovative, effective, and efficient design and analytic methods for HIV prevention studies; (iii) performs analysis and interpretation of study data in

collaboration with network investigators; and d. provides statistical input to the development, implementation and operation of data management and quality control procedures.

Operations Department

The Operations Department consists of 4 Sections. Members of these Sections include all the staff responsible for data entry and data quality control, the protocol programmers, the clinical data monitoring staff and the special projects section. Special project management is staffed by a small number of senior project managers responsible for the development of systems, tools, documents, etc. that are not study related. This Department: (i) Performs all aspects of data flow management—from the time data enters the SDMC as a DataFax image to the time data resides in the SAS database including performing all data entry, producing data QC reports to the sites and resolving errors; (ii) Provides database management and production of routine study monitoring reports; (iii) Develops and maintains clinical safety monitoring programs and safety reports; (iv) Develops and supports the statistical database and the laboratory specimen tracking system, and (v) Monitors clinical safety reports for Protocol Safety Teams and codes adverse experiences reported on CRFs using MedDRA.

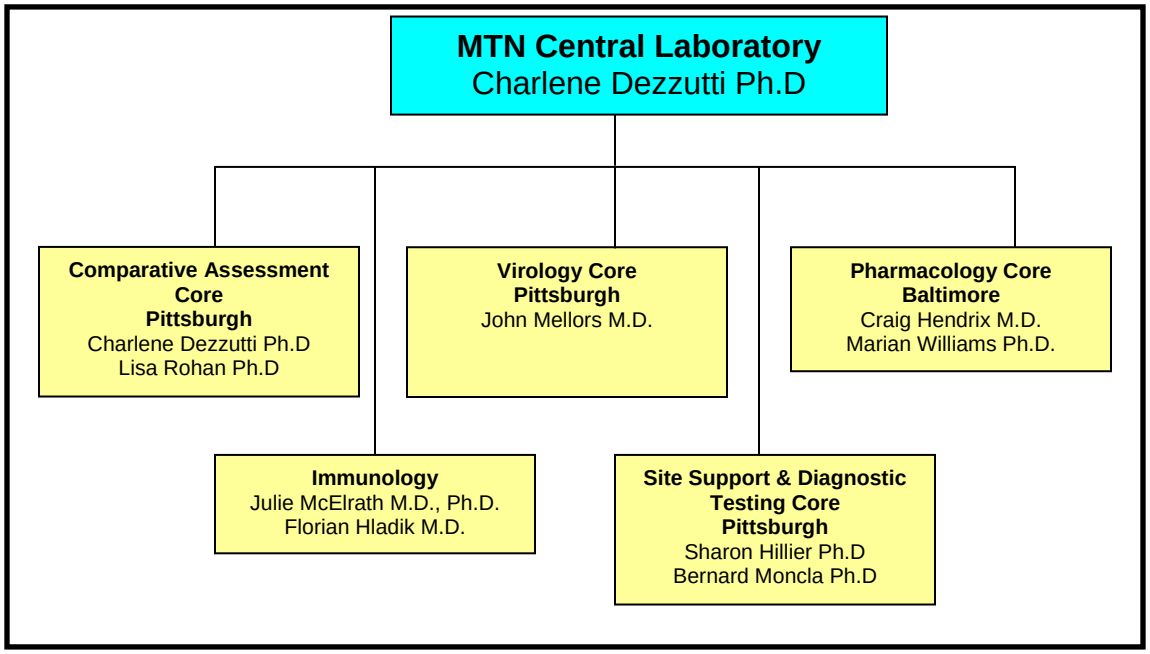
Shared Resources Department

The Shared Resources Department contains Sections that support departmental infrastructure. The responsibilities include (i) providing administrative support including personnel, payroll and facilities management; as well as fiscal oversight; (ii) designing and producing all study materials, including CRFs in 17 different languages; (iii) designing and maintaining the internal Web site and support Network specific web servers; (iv) installing and maintaining all work stations and servers required to support the DataFax systems as well as the PC and UNIX Network within the SDMC; e. building and maintaining data security requirements, including systems responsible for daily data backups and firewall construction and maintenance; and (v) deploying and maintaining DataFax and Internet fax-relay systems at all US and non-US sites.

MTN Central Laboratory

The MTN Central Laboratory key personnel are presented in Figure 6 below:

Figure 6. MTN Central Laboratory Organizational Structure



The specific aims of the MTN CL are the following:

- Provide laboratory-based scientific leadership and consultation to the MTN, collaborating organizations, and protocol teams.
- Participate in the MTN protocol development and review process.
- Participate in the MTN Executive Committee.
- Provide processing, storage, and retrieval of domestic and international MTN clinical trial specimens.
- Provide quality assurance (QA) for specimen processing, assay performance, and specimen related data transmission performed at each MTN Clinical Trials Unit (CTU).
- Provide training and infrastructure support in laboratory QA, assay performance, and specimen shipping procedures at the CTU laboratories.
- Perform comparative assessment, virologic, microbiologic, immunologic, and pharmacologic testing for the MTN protocols.
- Modify assays for use in the MTN clinical trials.
- Coordinate procedures and transmission of timely, accurate laboratory data to the MTN SDMC.
- Coordinate cross-network CL collaborations.
- Publish findings of product assessment, assay evaluation, and evaluation of safety and inflammation biomarkers.

The investigators described in this section will provide the expertise for the laboratory support needed for the successful execution of the MTN scientific agenda. These individuals and their laboratories will support the scientific agenda and the conduct of microbicide trials as follows:

- Provide training at CTU laboratories for safety, Good Clinical Laboratory Practice (GCLP), routine (e.g. hematology, HIV serology, etc.) and specialized (e.g. PBMC processing, etc.) laboratory assays, specimen handling and shipment.
- Provide QA/QC that the CTU laboratories are proficient at performing the tasks mentioned in #1. This will include end-point validation.
- Provide comparative assessment of microbicide candidates to ensure the most efficacious and least toxic products are advanced to clinical trial.
- Provide virologic, bacteriologic, immunologic, and pharmacologic assays that are not routinely available at the CTU sites.
- Modify and validate assays such as those to measure infectious virus, drug absorption assays, and cytokine bead arrays for use in support of MTN trials.
- Support the MTN through involvement at the protocol development and implementation stages. This involvement may include participation on protocol team conference calls, writing and/or reviewing specific protocol sections, testing of protocol samples, writing relevant sections of papers for publication. A portion of this function will be to coordinate with the protocol teams and the MTN SDMC the type of specimens, schedule of collection, and reporting of results in a standardized manner across protocols.
- Support the MTN by providing scientific leadership at the level of the Executive Committee and Cross-Network CL where the scientific agenda is developed, reviewed, and approved for implementation.
-

iii. Key Personnel

The MTN key personnel are listed in the Leadership Table 2 and presented in Figures 2, 4, and 8.

iv. Coordination

In addition to the above activities, it is recognized that there are a broad range of entitles involved in microbicide research internationally. It is critical that activities of the MTN be complementary rather than duplicative of that being conducted by other network groups. During January of 2005, representatives of CONRAD, USAID, The International Partnership for Microbicides, the Gates Foundation, the Medical Research Council, the International Working Group on Microbicides, the World Health Organization, the Foundation for AIDS Research, and the Centers for Disease Control were contacted regarding their participation in the MTN

Liaison Committee. These groups have agreed to meet with MTN Leadership at 6 month intervals to share information regarding clinical trial activities, availability of clinical trial populations, information from interactions with regulatory agencies, approaches to working with communities, and coordination of clinical trials portfolios.

By meeting frequently and openly to discuss the microbicide trials which are ongoing under the direction or through funding by each of the above named groups, it is anticipated that the DAIDS funded microbicide research agenda can be better integrated and understood by the larger research community engaged in microbicide research.

Cross-Network Collaborations

The MTN leadership recognizes clearly the need to coordinate, and whenever possible, collaborate with other DAIDS sponsored networks and agencies working in the microbicide development field. Summarized below are the cross-network collaborations, which have been identified and agreed upon by other network leaders to date.

Table 6. MTN Collaborative Relationships with Other Networks

Group	MTN
DAIDS Network Coordinating Committee	CORE and Central Lab leadership have participated in the network coordination meetings and phone calls since December 2004. Plans to support the continued activities of the network coordinating group included in the CORE application.
Vaccine Trial Network	Julie McElrath, PI of the VTN Central Laboratory will be the PI of the Immunology CORE of the MTN Central Laboratory. Coordination of Community Advisory Group Activities with Steve Wakefield and his colleagues at the VTN.
HPTN	Will utilize the HPTN Behavioral CORE under the direction of Dr. Tom Coates. MTN will utilize the Ethics CORE of the HPTN, under the direction of Dr. Sugarman.
AACTG	MTN will include the Chair of the Women's Committee as a non-voting member of the Executive Committee. MTN and AACTG will collaborate whenever possible in coordinating care for HIV infected individuals at domestic and international sites to MTN sites which are also AACTG sites or where sites are available in the same geographic location.
Sexually Transmitted Infection Clinical Trials Group (funded by DMID/NIAID)	Nancy Padian, a member of the Executive Committee of the STI CTG is the Chair of the Use of Barriers with Microbicides Group of the Science Committee of the MTN. In addition, Drs. Hillier and McGowan are site PI's for Pittsburgh and Los Angeles, respectively for the STI CTG.
Adolescent Trial Network	The MTN proposes to conduct at least one study (MTN-013) for high risk adolescents with the Adolescent Trial Network. Pamina Gorbach, the Chair of the MTN Behavioral and Social Science Research Group also serves on the ATN Community Prevention Leadership Group.

Industry

The microbicide pipeline is critically dependent on the identification and development of new candidate microbicides. It is anticipated that the vast majority of candidate microbicides will be generated within the Pharmaceutical Industry. The MTN Industry Liaison Committee (ILC) will be the primary focus for the coordination of communication with Industry. In addition to provision of products for ongoing studies, the ILC will also work proactively to encourage Industry to provide access to new candidate microbicides.

Community

Experience over the past years has taught the HIV prevention community, that inclusion of the community broadly defined, in every stage of protocol development, implementation, and eventual release of the data is essential. The MTN CORE will work closely with the Community Advisory Groups at each of the clinical trial sites as well as with the Community Advisory Board Leadership at other networks to develop and implement

effective, timely community involvement. Stella Kirkendale of Family Health International has been involved intimately in the development of Community Advisory Board Support and regional support for microbicide trials. She will continue this activity through the FHI CORE over the course of the MTN. In addition, we have partnered with the Vaccine Trial Network to develop materials for the community groups explaining prevention research and in engaging community leaders in informing researchers regarding community values and the planned trials.

In addition to focused efforts to engage community members of potential trial participants, the MTN proposes an innovative strategy of engaging medical leaders in providing community input into the MTN agenda. The regional clinical managers under the direction of Connie Celum will be engaged in supporting clinical trial site investigators in preparing the local medical community for the impact of planned studies. By working with local and regional African-based physicians, it is hoped that the MTN can better communicate to both medical leaders and physicians in the impacted communities the MTN studies and the safety measures that have been incorporated to protect the safety of all trial participants. Further, release of information regarding safety or responses to activists should be coordinated through these regional medical physicians.

v. Special Features

Drug Development Paradigm

In the absence of a commitment from the Pharmaceutical Industry to develop microbicides, there is an urgent need for the United States Public Health Service to assume scientific leadership in this area. To date, the majority of microbicide development has occurred in a fragmented fashion. As a consequence, progress has been complex and slow. The fundamental goal of the MTN is to establish an efficient mechanism to take candidate microbicides from the preclinical phase through to licensure. The MTN intends to focus on candidate microbicides that have been shown to work through specific activity against HIV. The MTN differs from most NIH funded networks in that it is focused on drug development rather than pathogenesis. The MTN scientific agenda is geared towards maximizing the efficiency of microbicide development.

Regional Support for MTN Trials

The ultimate goal of the MTN is to progress a candidate microbicide to licensure by the FDA. Inevitably, the majority of efficacy studies will be conducted in the developing world. Experience has shown that many sites in this region of the world are ill equipped to conduct registrational trials with the degree of regulatory, clinical, and laboratory rigor required to support drug licensure. As a consequence, the MTN has committed to provide developing world sites with adequate clinical, regulatory, pharmacy, and laboratory support to ensure the quality of clinical trial conduct needed. This support includes regional physicians, clinical support staff, and regional laboratory managers based in the developing world. In addition, the core has included pharmacy and regulatory support to assist the sites at all stages of protocol development and implementation. Although this level of support may appear financially prohibitive, the levels of support being proposed represent a modest investment compared to industry standards of drug development where it has been estimated that the costs of developing a new chemical entity is in the region of $800 million dollars.

Central Laboratory

Over 60 products are entering the microbicide pipeline. Initial work with nonoxynol-9 containing products, an approved over-the-counter spermicide, demonstrated that choosing a convenient, available product is not the best approach to product selection. Early in vitro activity suggested that nonoxynol-9 would be effective against HIV-1 and other sexually transmitted pathogens and may have a benefit if used as a topical microbicide. However, subsequent clinical trials showed that nonoxynol-9 caused extensive epithelial disruption and inflammation of the genital tract. More importantly there was evidence of increased HIV-1 transmission during use of nonoxynol-9-containing products. Because of this poor showing, there is a necessity that we do not repeat the mistakes made in choosing another “nonoxynol-9” product in terms of bringing a non-efficacious,

toxic product to clinical trial. Therefore, a comprehensive, comparative microbicide assessment is required to ensure that only the most effective, nontoxic products re brought forward to clinical trial.

In addition to providing clinical trial support, an emphasis of the MTN Central Laboratory (CL) will be contributing to optimal product selection. Because the most important aspect of a clinical trial is the candidate being tested, the MTN CL will provide a comprehensive microbicide assessment using existing, standardized protocols, which will predict toxicity, efficacy, and acceptability. Each of the core components (Comparative Assessment, Pharmacology, and Virology) will provide information to the Product Selection Committee to make the final informed determination of which product will move to Phase I trial. The information provided will highlight areas of product-specific attributes or components that will need to be incorporated at the onset of clinical evaluation (e.g. the development of drug-specific resistance mutations). Collectively, these data will streamline product selection and move the most efficacious and least toxic product to clinical trial in a timely fashion.

The Comparative Assessment Core will evaluate each new product candidate against representative products such as N9, hydroxyethyl cellulose, for its ability to prevent infection against a broad range of cell-free and cell-associated primary HIV subtypes. This activity along with potential acute and long-term toxicity, and adsorption and permeability of the candidate into mucosal tissues will be tested using relevant tissue explant cultures. Tissue explant cultures offer a bridge from in vitro assessment to clinical testing. A unique aspect of this Core will be the ex vivo assessment of factors likely to impact the candidate acceptability such as spread (leakiness) and consistency. All of the Comparative Assessment Core activities will be coordinated with the Pharmacology and Clinical Cores for validation of these assays. The Pharmacology Core will evaluate the product absorption after vaginal application and distribution in vaginal, cervical, and endometrial tissue prior to standard Phase I studies. These pre-Phase I studies will provide valuable information regarding dosing regimens, macroscopic and microscopic distribution and clearance of the product from sites of transmission. The Virology Core will provide a valuable service by evaluating each candidate for the development of drug-resistant variants prior to Phase I study. The selection and characterization of drug resistant HIV-1 in vitro will help predict the type of drug-resistant viruses that may emerge during trial use.

Because initiation of a clinical trial with an inappropriate product would be extremely costly both financially and time lost in delaying effective HIV prevention, the Comparative Product Assessment Core will provide a report of the product's advantages and disadvantages to the Product Selection Committee to decrease that likelihood. By ensuring that the most efficacious, nontoxic, and acceptable products are brought forward, this Assessment Core will help to streamline the selection process. Moreover, the information obtained from this assessment will serve to identify product-specific components, which may need to be incorporated at the onset of clinical evaluation.

The results of the Comparative Product Assessment Core will be provided to the manufacturer to supply them the attributes that were advantageous or non-advantageous so they may potentially modify their product accordingly for future reevaluation by the CL. This will allow us to provide the manufacturer valuable information that they may not have ability to generate and will ultimately provide the microbicide community with better candidates. The Comparative Assessment, Pharmacology, and Virology Cores provide a cornerstone of the MTN CL strategy which will ensure that the women who volunteer for participation in MTN studies have the highest likelihood of having access to safe and effective products. The data derived from these extensive evaluations can be used as potential predictors of safety and effectiveness in clinical trials. This would provide an enormous benefit to the field of microbicide research.